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Patrícia de Jesus Castro Sousa

Prevenção da Infeção Periconcecional por CMV em Portugal: estudo de subgrupo populacional em estabelecimento hospitalar da área metropolitana do Porto

Periconceptional CMV Infection Prevention in Portugal: population subgroup study in a hospital of the metropolitan area of Porto

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TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Prevenção da Infeção Periconcecional por CMV em Portugal: estudo de subgrupo populacional em estabelecimento hospitalar da área metropolitana do Porto

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Doutor Fernando Gabriel Rodrigues da Costa Madureira

COORIENTADOR (se aplicável)

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Abstract

Currently in Portugal, universal screening of pregnant women for Cytomegalovirus (CMV) infection is not performed. However, it is recommended to screen all women attending preconception care.

We aimed to assess women's attendance to preconception care and if their serologic status regarding CMV was known and/or investigated in that consultation.

In this cross-sectional study, we interviewed 240 women admitted to the obstetrical ward of a hospital in the Metropolitan Area of Porto (Portugal) about their adherence to preconception care and collected data regarding their CMV serologic status and its investigation.

We found that 71,3% of the women who attended preconception care were not screened for CMV infection. Among primigravida, the screening rate was only of 30,4% (upper limit of CI95%: 44,8%). There were no statistically significant differences between the private and public sectors of healthcare. We observed attendance to preconception care is high (73,1%). For the population subgroup of the metropolitan area of Porto, attendance to preconception care is at least 66%, with a 95% confidence level.

Portuguese guidelines stating a woman's serologic status regarding CMV should be investigated in preconception care are not properly implemented. This suggests guidelines should assure the screening of previously non-screened women during pregnancy.

Introduction

Cytomegalovirus (CMV) causes the most prevalent congenital infection[1]. It belongs to the herpesviridae family and can be spread through body fluids such as saliva, urine, blood or genital secretions[2, 3]. The most important infectious source consists of toddlers attending day care[2]. Both primary and secondary infections can be vertically transmitted[4], although primary infections are thought to have a higher rate of transmission to the fetus[5]. When a CMV infection occurs in the mother, the placenta may become dysfunctional and fail to properly nourish and oxygenate the fetus[4], causing severe illness[5]. In fact, this infection is the first non-genetic cause of sensorineural hearing loss in newborns and the primary cause of congenital neurological handicap of infectious origin[2, 3].The earlier in pregnancy the infection occurs, the higher the rate of vertical transmission[6] and the more severe the complications to the fetus[2, 7].

CMV congenital infection affects 0,6-0,7% of all newborns[2, 8]. 40-65% of women of reproductive age are at risk for primary infection[9]and 0,6-1,4% are primarily infected with CMV during pregnancy[2]. Primary infection is usually asymptomatic, with fewer than 5% of pregnant women showing symptoms. Even when present, they are usually nonspecific[2]. This makes testing women upon clinical suspicion very inefficient. Pregnant women are also tested when consistent abnormalities are found in the ultrasound. However, Guerra *et al* concluded that when fetal infection status is unknown, ultrasound abnormalities predict symptomatic congenital infection in only 35% of cases[10]. This infection is difficult to prevent since we are dealing with a ubiquitous virus[5]. The development of a vaccine is of high importance, since its needed investment is estimated in US $360 million, whereas providing care for children with

congenital CMV infection amounts to $1.9 billion per year[3]. In spite of this, the availability of a CMV vaccine is at least 6-10 years away[11].

Whether all pregnant women should or should not be screened is a highly-debated question[4]. Currently in Portugal the official recommendation is not to universally screen pregnant women for CMV infection, though it is recommended that women in preconception care be screened[12]. There are two main arguments supporting this decision[13]: one is the uncertainty of a bad prognosis for the infected fetuses, since 90% are asymptomatic at birth. Yet 15% of these develop symptoms later on[8]. The other is the lack of an approved treatment to be offered after a diagnosis is made[13, 14]. However, that paradigm is changing. Several studies have suggested the administration of CMV hyperimmune globulin during pregnancy may be associated with better outcomes in fetuses suspected of having congenital CMV infection[15, 16, 17]. Also, Leruez-Ville *et al* recently published their results showing valacyclovir (8g/day) given in pregnancy significantly increased the proportion of asymptomatic newborns from 43% without treatment to 82% with treatment. All 33 children who were asymptomatic at birth remained asymptomatic at 12 months of age[18, 19]. Valacyclovir has the best safety profile of the anti-CMV drugs and its administration in the first trimester was not associated with an increased risk of major birth defects[20]. This high dosage was extremely well tolerated both laboratorial and clinically, with an adherence to treatment over 90%[18]. Also, a recent study found that universal serologic screening (as opposed to screening only high-risk women or those with abnormal ultrasound findings) was the preferred and most cost-effective approach, as long as the treatment was effective in 47% of the cases[1]. In spite of the recommendations, many doctors in Portugal screen asymptomatic women during pregnancy[4].

Since universal screening during pregnancy is not recommended, the efficacy of

preconception screening is of paramount significance. Knowing women's serologic status prior to pregnancy allows for preventive care and facilitates an early-on diagnosis of a CMV infection during gestation.

In this study, we investigated the success of preconception care in the metropolitan area of Porto, regarding women's adherence and the investigation of their CMV serologic status prior to pregnancy.

Methods

Study Design and Participants

In this cross-sectional study, we approached 240 pregnant and puerperal women admitted to the Obstetrics ward of a hospital in the metropolitan region of Porto (Portugal) and collected data regarding their age, education level, marital status, number of pregnancies and deliveries, and whether the current pregnancy was planned. If so, we asked if they attended preconception consultation and in which setting. We then investigated if their serologic status regarding CMV was previously known and/or investigated in that consultation. In marital status, unmarried couples are defined as two people living together for over two years.

Data were collected from September 9th to November 28th 2016 by interviewing women in person and consulting their Pregnant Woman's Health Booklet or electronic clinical records. We included all patients staying in the ward and able to respond at the time of visit, as long as informed written consent was provided. Ward visiting days were chosen by convenience, with caution to select different weekdays. Women under the age of 18 were excluded. This study was approved by the institution's' Ethics Committee.

Data Measurement

Maternal educational status (ES) was stratified in 4 strati, according to completion of:

- no education, primary education, or lower secondary education (ES 1);
- upper secondary education (ES 2);
- post-secondary non-tertiary education (ES 3);
- tertiary education (ES 4).

Consultation settings were described as: PbGP - Public General Practitioner; PvO - Private Obstetrician and PbO – Public Obstetrician. PvO setting corresponds to women who attended only the private sector. For women who attended both, only the information regarding the public sector is considered.

Statistics

Data analysis was performed using IBM SPSS Statistics 23 software and statistical software package R, version 3.3.2.

Maternal age was reported as median (interquartile range); all other variables were categorical and are reported as absolute or relative frequencies.

Comparisons

The participants were compared according to pregnancy planning. Planned pregnancies were compared according to attendance to preconception care and preconception consultation setting.

For comparisons of distributions between groups, the Mann-Whitney and Kruskal Wallis tests were used for maternal age and for ordinal variables (gravidity, parity and educational status). When assumptions for the first weren’t verified, Pearson Chi-Square or Fisher's Exact Test were used for all other variables, reporting the 95% confidence

interval for the proportions derived from Wilson method[21, 22]. p-values <0.05 were considered statistically significant.

Results

Baseline characteristics

For the 240 pregnant and puerperal women included, median age was 32 years, with an interquartile range of 27 to 36 years. Of the 240 women, 171 had a planned pregnancy and of these, 125 attended preconception care. Of the 46 that did not attend, 35 (76,1%) were not interested in preconception consultation and 11 intended to attend. Information regarding CMV serologic status was accessible in electronic records for all women who chose the public setting. For the women who attended the private setting, Pregnant Woman's Health Booklet was the only available source, but only 25 (59,5%) of the private setting consultations had record of the CMV serologic status. The complete data set was available for 45 primigravida (42,9% of the 105 primigravida included).

Attendance to preconception care was 73,1% (CI95%: 66.0-79.2%) and 79.5% (CI95%:72.9-84.9%) including women who intended to attend but conceived before they had the opportunity to (Table 1).

Pregnancy planning

71,3% of all pregnancies were planned. A chi-square test was performed and a significant association was found between parity and marital status, and pregnancy planning: $X^2(2, N = 240) = 8,193$ and 15,345, p=0,042 and 0,002, respectively. There was a higher proportion of women with a parity of 3 or more in the unplanned pregnancy group, as

opposed to the planned pregnancy group; no association was found between gravidity or educational status and the planning of the pregnancy: $X^2(2, N = 240) = 2,112$ and 6,691 p=0,348 and 0,082, respectively.

The categories with higher relative frequency for gravidity, parity, educational and marital status in not vs planned pregnancy were 1 vs 1, 1 vs 1, ES2 vs ES3 and single vs married, respectively. Since gravidity, parity and educational status are ordinal variables, we also performed a Mann-Whitney test to evaluate these variables' distribution. The two groups differed significantly in educational status distribution (Mann–Whitney U = 4894, n1 = 68 n2 = 171, p<0.05 two-tailed), and maternal age (Mann–Whitney U = 4080, n1 = 68 n2 = 171, p<0.001 two-tailed) with women who planned the pregnancy being older and having a greater mean rank than the ones with an unplanned pregnancy (126,38 vs 105,93) (Table 2).

Preconception care

Fisher's exact test, two-tailed, was performed and a significant association was found between educational and marital status, and attendance to preconception care, p<0,001 and <0,05, respectively). Based on Mann-Whitney, these groups also differed significantly with respect to maternal age (Mann–Whitney U = 1750,5, n1 = 125 n2 = 115, p< 0.001, two-tailed). (Table 2).

Based on bivariate analyses, PbGP and PvO settings differed significantly with respect to maternal age (Mann–Whitney U = 1009,5, n1 = 73 n2 = 42, p = 0.002 two-tailed) and educational status (Fisher's exact test, p=0.002 two-tailed), with PvO setting having older individuals, with a higher education status.

There were no significant differences in the distribution of gravidity and parity between all preconception care settings. All differences between PbGP and PbO were

nonsignificant.

There's a tendency for different distributions of education and marital status between PvO and PbO groups ($p<0.1$ applying Fisher's Exact Test), with PbO having a tendency for lower ES and more unmarried couples. These differences might be nonsignificant because of the small sample size (higher sample power = 47,6%). (Table 2).

CMV serologic status

A total of 108 women had attended preconception care and had Pregnant Woman's Health Booklet or electronic clinical records filled in. Of these, 20 had a previously known serologic CMV status. Of the 20 with previously known serologic CMV status, 4 (20%) hadn't had previous contact with the virus, and only 2 were screened before the current pregnancy. Of the 16 who had previous contact with CMV, only 1 (6.3%; CI95%: 1.1-28.3%) was screened prior to the current pregnancy.

Screening rate for those with previously unknown serologic status was 31.8% (CI95%:23.0-42.1%).

Screening rates did not differ significantly among pre-conception care settings. For all settings, 71.3% (CI95%: 62.5-79.0) of the women weren't screened, and among primigravida screening rate did not reach 31% (CI95%: 19.1 – 44.8%); the highest screening rate for primigravida occurred in the PbGP setting (33,3%) (Table 3).

Discussion

We found that 71,3 % of all women with available data were not screened for CMV infection in preconception care. This is a very clinically relevant proportion considering

the guideline in Portugal states that every woman who attends preconception care should be tested for CMV infection. We found no statistically significant differences in screening rates among pre-conception care settings. This could suggest both general practitioners and obstetricians are similarly aware of CMV screening in preconception care. However, 40% of women who attended the private sector didn't have this information filled in in the Pregnant Women's Health Booklet, so it is possible the screening was preformed but not registered. Moreover, 68,2% of women whose serologic status regarding CMV was unknown were not screened and 2 of the 4 women who were seronegative in the last test were not tested again before the current pregnancy. Looking at the primigravida group, for whom this preconception consultation was the first opportunity to be tested, we find that the general screening rate was only of 30,4% (upper limit of CI95%: 44,8%), with a higher screening rate in the PbGP setting, although there is no significant difference from other settings. This means the screening rate for primigravida is under 50%.

We observed that attendance to preconception care is high (73,1%) and even higher including women who intended to attend but conceived before they had the opportunity to (79,5%). We can conclude that for the population subgroup of the metropolitan area of Porto, attendance to preconception care is at least 66%, with a confidence level of 95%.

An unexpected finding was that the CMV serologic status in preconception consultations was only filled in in 57% of the investigated Pregnant Woman's Health Booklets. These results refer to the private setting, since we only checked the booklets of the women who chose exclusively this sector.

In our study, women who attend preconception care are older, more frequently married and have a higher education status. The same characteristics are associated with women who planned the pregnancy. Other studies have shown higher education levels are

associated with lower CMV seroprevalence[9]. Planned pregnancies are also associated with parity, seeing that this group has a lower frequency of women with a parity ≥ 3 than the unplanned group.

No significant differences were found between the PbGP and PbO groups for any of the characteristics assessed, likely due to the small sample size in the PbO group.

Our research is not without limitations. Sampling was performed with a nonprobability method of convenience. However, we attempted to minimize selection bias by choosing different weekdays for ward visiting. For some of the sub analyses, sample size was small. However, for our main outcome (prediction of screening rate for women who attended preconception care) sample power was over 90%, with a significance level of 0,05. Some of the women included in the "single" marital status may relate to women living together with their partners for under 2 years.

Given the current situation, where universally screening pregnant women for CMV infection is not recommended, testing women in preconception care is fundamental, so doctors pay more attention to suggestive symptoms and a primary infection may be detected early on[13]. Our findings reveal the current strategy is not efficiently implemented. This raises the question of whether women who are not screened in preconception care should be screened in the first consultation during pregnancy.

Disclosure of interest

The authors report no conflicts of interest.

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Table 1. Demographic and Clinical Characteristics of Participants

	N	TOTAL SAMPLE
TOTAL	240	240
MATERNAL AGE (years)	240	32 (27 – 36)
GRAVIDITY	240	
• 1		105 (43,8)
• 2		80 (33,39)
• 3+		55 (22,9)
PARITY	240	
• 0		12 (5)
• 1		126 (52,5)
• 2		84 (35)
• 3+		18 (7,5)
PLANNED PREGNANCY	240	171 (71,3)
PRECONCEPTION CARE	171	
• **YES**		125 (73,1)
Public General Practioner (PbGP)		73 (58,4)
Public Obstetrician (PbO)		10 (8)
Private Obstetrician (PvO)		42 (33,6)
– CMV STATUS FILLED IN	42	25 (59,5)
• **NO**		46 (26,9)
– Motive		
Not interested		35 (76,1)
Intended to		11 (23,9)
EDUCATION STATUS*	240	
ES 1		69 (28,7)
ES 2		70 (29,2)
ES 3		82 (34,2)
ES 4		19 (7,9)
MARITAL STATUS	240	
Single		93 (38,8)
Married		98 (40,8)
Unmarried couple		39 (16,3)
Divorced		10 (4,2)

Maternal age is presented as median (interquartile range), the other variables as numbers (%).
*ES 1- no education, primary education, or lower secondary education; ES 2 - upper secondary education; ES 3 - post-secondary non-tertiary education; ES 4 - tertiary education.

Table 2. Association Between Demographic/Clinical Characteristics and Pregnancy Planning, Healthcare Setting and Attendance to Preconception Care

	PREGNANCY PLANNING				**HEALTHCARE SETTING**				**ATTENDANCE TO PRECONCEPTION CARE**		
	UNPLANNED PREGNANCY	PLANNED PREGNANCY	X2 P VALUE	MANN-WHITNEY p VALUE	PbGP	PvO	PbO	p VALUE	YES	NO	p VALUE
TOTAL (n=240)	69 (28,7)	171 (71,3)			73 (58.4)	42 (33.6)	10 (8.0)		125 (73.1)	46 (26.9)	
MATERNAL AGE (years)	29 (23-34)	33 (29-36)		**<0,001	*33 (29.5-35.5)*	34 (32-38)	32 (29.5-35.5)	*0.002	33 (31-36)	29 (24-34)	**<0,001
GRAVIDITY			0,348	0,270					1 (42.4)	1/2 (37.0)	0,791
• **1**	35 (50,7)	70 (40,9)			**33 (45.2)**	**17 (40.5)**	3 (30.0)				
• 2	19 (27,5)	61 (35,7)			27 (37.0)	13 (31.0)	**4 (40.0)**				
• 3+	15 (21,7)	40 (23,4)			13 (17.8)	12 (28.6)	3 (30.0)				
PARITY			[a]0,042	0,342					1 (52,2)	1 (52,2)	0,1827
• 0	2 (2,9)	10 (5,8)			5 (6.8)	2 (4.8)	3 (30.0)				
• **1**	37 (53,6)	89 (52,0)			**40 (54.8)**	**21 (50.0)**	**4 (40.0)**				
• 2	23 (29,0)	64 (37,4)			25 (34.2)	17 (40.5)	3 (30.0)				
• 3+	**10 (14,5)**	**8 (4,7)**			3 (4.1)	2 (4.8)	0				
EDUCATION STATUS [c]			0,082	*0,030	#		[b]	#0.002 [a]0.083	ES3 (42,4)	ES1 (54,3)	**/## <0,001
ES 1	23 (33,3)	46 (26,9)			18 (24.7)	1 (2.4)	2 (20.0)				
ES 2	**25 (36,2)**	45 (26,3)			**23 (31.5)**	10 (23.8)	**4 (40.0)**				
ES 3	19 (27,5)	**63 (36,8)**			**24 (32.9)**	**25 (59.5)**	**4 (40.0)**				
ES 4	2 (2,9)	17 (9,9)			8 (11.0)	6 (14.3)	0				
MARITAL STATUS			[a]0,002		[b]			[a]0.052	Married (53,6)	Single (47,8)	#0,021
Single	**39 (56,6)**	54 (31,6)			23 (31.5)	8 (19.0)	1 (10.0)				
Married	17 (24,6)	**81 (47,4)**			**34 (46.6)**	**29 (69.0)**	**4 (40.0)**				
Unmarried couple	9 (5,8)	30 (3,5)			13 (17.8)	4 (9.5)	**4 (40.0)**				
Divorced	4 (13,0)	6 (17,5)			3 (4.1)	1 (2.4)	1 (10.0)				

Maternal age is presented as “median (interquartile range)”, the other variables as “number (%)”. For attendance to preconception care, the category with higher relative frequency is presented (%).

[a]p<0.05, applying chi-square test X^2; *p<0.05 and **p<0.001, applying Mann-Whitney test; [b]p<0.1, #<0.05 and ## p<0.001 applying Fisher’s exact test. In “Healthcare setting” comparison, values are significantly different compared to PvO group. All differences between PbGP and PbO were nonsignificant. Attending and non-attending groups did not differ significantly in gravidity and parity.

[c] ES 1- no education, primary education, or lower secondary education; ES 2 - upper secondary education; ES 3 - post-secondary non-tertiary education; ES 4 - tertiary education.

Table 3. Screening Rates.

	Total	Screened	CI95 - Lower Limit	CI95 - Upper Limit
Available data	108	31 (28.7%)	21.0	37.9
• **PbGP**	73	21 (28.8)	19.7	40.0
• **PvO**	25	8 (32.0)	17.2	51.6
• **PbO**	10	2 (20)	5.7	51.0
Primigravida	46	14 (30.4)	19.1	44.8
• **PbGP**	33	11 (33.3)	19.8	50.4
• **PvO**	10	3 (30.0)	10.8	60.3
• **PbO**	3	3 (100)	43.9	100
Previously known	20	3 (15.0)	5.2	36.0
• No Previous Contact	4	2 (50.0)	15.0	85.0
• Previous Contact	16	1 (6.3)	1.1	28.3
Previously unknown	88	28 (31.8)	23.0	42.1

Screening rates are presented as “number (%)”. CI95 – 95% confidence interval for the screened proportion derived from Wilson method. All differences among preconception care settings were nonsignificant.

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Parecer da Comissão de Ética para a Saúde do
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da Universidade do Porto

146-16

Unidade de Investigação

Tomei conhecimento. Nada a opor.

13 de Junho de 2016

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

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13 JUN 2016

Aprovado. Ao CA.

(Prof.ª Doutora Ana Azevedo)

AUTORIZADO

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Exmo. Senhor
Presidente do Conselho de Administração do
Centro Hospitalar de S. João – EPE

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: Patrícia de Jesus Castro Sousa

Título do projecto de investigação: "Prevenção da Infeção Periconcecional por CMV em Portugal"

Pretendendo realizar no(s) Serviço(s) de Ginecologia e Obstetrícia do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 27 / Abril / 2016

O INVESTIGADOR/PROMOTOR

Patrícia Sousa

SÃO JOÃO
HOSPITAL

Comissão de Ética para a Saúde do HSJ

Parecer

Projeto intitulado: "Prevenção da Infeção Periconcecional por CMV em Portugal"

Estudo que pretende vir a ser desenvolvido no Serviço de Ginecologia e Obstetrícia do CHSJ pela aluna do MIM da FMUP Patricia de Jesus Castro Sousa, tendo como orientador o Dr. Gabriel Madureira e elo de ligação a Drª Marina Moucho.

Do ponto de vista científico, trata-se de um estudo em que a investigadora se propõe avaliar a realidade de prevenção da infeção por CMV nos cuidados preconcecionais em Portugal. Para o efeito está prevista a realização de um questionário anonimizado do qual se anexa a respetiva cópia.

Não estão previstos benefícios, riscos ou incómodos para as participantes, para além do tempo dispendido na resposta ao questionário.

Está previsto o acesso a dados clínicos dos doentes pela investigadora, através do elo de ligação.

Está prevista a obtenção de consentimento informado que é acompanhado de uma informação para a participante, esclarecedora sobre a natureza do estudo e que contempla as questões éticas relevantes.

A investigadora dispõe da competência científica para realização do estudo, que está autorizado pelo diretor do Serviço de Ginecologia e Obstetrícia.

O estudo não é financiado e não prevê a realização de exames complementares nem a necessidade de seguro.

Em face da análise do protocolo proponho a sua aprovação pela CES do CHSJ.

Porto, 12 de maio de 2016

O relator

Prof. Manuel Pestana

O título a propor deverá ser adequado para a adaptação ao objectivo do estudo

13.05.2016

Em face da apreciação da investigadora proponho a aprovação do estudo pela CES do CHSJ

Manuel Pestana
NEFROLOGIA
19987

9.06.2016

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)

NÃO ☐

NÃO APLICÁVEL ☒

8. TERMO DE RESPONSABILIDADE

Eu, Patrícia de Jesus Castro Sousa, abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 28 / 04/ 2016

A Comissão de Ética para a Saúde tendo aprovado o parecer do Relator, aguarda que o Investigador/Promotor esclareça as questões nele enunciadas para que possa emitir parecer definitivo.

Patrícia Sousa

O Investigador Principal

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

2016.05.13

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO/FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

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.Centro Hospitalar **São João**.

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___/___/___

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética